Circulation: Heart Failure

ORIGINAL ARTICLE

Effect of Baseline Left Ventricular Ejection Fraction on 2-Year Outcomes After Transcatheter Aortic Valve Replacement

Analysis of the PARTNER 2 Trials

BACKGROUND: Impaired left ventricular function is associated with worse prognosis among patients with aortic stenosis treated medically or with surgical aortic valve replacement. It is unclear whether reduced left ventricular ejection fraction (LVEF) is an independent predictor of adverse outcomes after transcatheter aortic valve replacement.

METHODS AND RESULTS: Patients who underwent transcatheter aortic valve replacement in the PARTNER 2 trials (Placement of Aortic Transcatheter Valves) and registries were stratified according to presence of reduced LVEF (<50%) at baseline, and 2-year risk of cardiovascular mortality was compared using Kaplan–Meier methods and multivariable Cox proportional hazards regression. Of 2991 patients, 839 (28%) had reduced LVEF. These patients were younger, more often males, and were more likely to have comorbidities, such as coronary disease, diabetes mellitus, and renal insufficiency. Compared with patients with normal LVEF, patients with low LVEF had higher crude rates of 2-year cardiovascular mortality (19.8% versus 12.0%, *P*<0.0001) and all-cause mortality (27.4% versus 19.2%, *P*<0.0001). Mean aortic valve gradient was not associated with clinical outcomes other than heart failure hospitalizations (hazard ratio [HR], 0.99; CI, 0.99–1.00; *P*=0.03). After multivariable adjustment, patients with reduced versus normal LVEF had significantly higher adjusted risk of cardiovascular death (adjusted HR, 1.42, 95% CI, 1.11–1.81; *P*=0.005), but not all-cause death (adjusted HR, 1.20; 95% CI, 0.99–1.47; *P*=0.07). When LVEF was treated as continuous variable, it was associated with increased 2-year risk of both cardiovascular mortality (adjusted HR per 10% decrease in LVEF, 1.16; 95% CI, 1.07–1.27; *P*=0.0006) and all-cause mortality (adjusted HR, 1.09; 95% CI, 1.01–1.16; *P*=0.02).

CONCLUSIONS: In this patient-level pooled analysis of PARTNER 2 patients who underwent transcatheter aortic valve replacement, baseline LVEF was an independent predictor of 2-year cardiovascular mortality.

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WHAT IS NEW?

- In contrast to prior reports, we showed in this study, based on a large adjudicated database using validated core lab analysis of echocardiograms of intermediate and high-risk patients enrolled in prospective trials and registries, that clinical outcomes after transcatheter aortic valve replacement with contemporary devices are dependent on baseline left ventricular ejection fraction.
- Each 10% (absolute) decrease of left ventricular ejection fraction below a left ventricular ejection fraction of 60% is associated with 16% increase in the risk of cardiovascular mortality within 2 years after transcatheter aortic valve replacement.
- A similar, although more modest, effect is seen with respect to all-cause mortality within 2 years after transcatheter aortic valve replacement.
- Mean aortic valve gradient was not found to be an independent predictor of 2-year all-cause and cardiovascular mortality.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The study challenges previous findings suggesting no prognostic role for baseline left ventricular ejection fraction in patients undergoing transcatheter aortic valve replacement.
- Early intervention for severe aortic stenosis before any decline in ventricular function might be beneficial, as the prognosis seems to worsen substantially with LV impairment.

Left ventricular (LV) dysfunction has been associated with poor prognosis among patients with severe symptomatic aortic stenosis (AS) who were treated conservatively with medical treatment.[1] Surgical aortic valve replacement (SAVR) has been shown to improve outcomes in this subset of patients,[2–4] although they still bear an increased mortality risk compared with patients with normal LV function.[5–8] Transcatheter aortic valve replacement (TAVR) is now an accepted alternative to SAVR in patients with symptomatic severe AS and intermediate[9,10] or higher[10–12] surgical risk and has demonstrated comparable outcomes to SAVR. However, there is conflicting information as to whether LV ejection fraction (LVEF) is an independent risk factor for poor TAVR outcomes. Data from a standard metanalysis that included findings from 6898 patients reported in 26 observational studies suggests that baseline LVEF holds predictive value with respect to cardiovascular and all-cause mortality, both in the short and long term.[13] However, a recent analysis of registry data from a large TAVR cohort suggested that, following adjustment to multiple risk factors, LVEF had no significant effect on outcomes and instead, baseline aortic valve gradient had a more significant effect on prognosis.[14]

We, therefore, sought to analyze the prognostic role of preprocedural LVEF on TAVR outcomes in a patient-level pooled analysis of patients with severe AS who were included in the PARTNER 2 trials (Placement of Aortic Transcatheter Valves).

METHODS

Data Sharing

Because of the proprietary nature of the data collected for this study, requests to access the dataset from qualified researchers only may be sent to the Scientific Publications Office of the trial sponsor (Edwards Lifesciences) at spo_thv@edwards.com.

Patients

Patient-level data from the PARTNER 2A and 2B randomized cohorts and the P2B and SAPIEN 3 nested registries were pooled in the current analysis. The design, eligibility criteria, and end points have been described in detail for each of the included studies.[9,15] Briefly, the PARTNER 2 trial included Cohort A, which enrolled patients with severe symptomatic AS at intermediate surgical risk at 57 sites in North America and randomized them to SAVR or to TAVR with the SAPIEN XT transcatheter heart valve and Cohort B, which enrolled inoperable patients in 28 sites in North America, and randomized patients to TAVR with either the SAPIEN or SAPIEN XT transcatheter heart valve, in addition to nested registries, which enrolled inoperable patients and focused on expanded valve sizes, alternative access routes, and valve in valve procedures; and 2 SAPIEN 3 cohorts, which enrolled inoperable, high-risk, and intermediate risk patients at 51 North American sites to be treated with the newest generation SAPIEN 3 transcatheter heart valve. All patients had severe, symptomatic AS. Key exclusion criteria included congenitally bicuspid aortic valve, severe renal disease, or LVEF <20%. Adverse events, including 2-year all-cause deaths and cardiovascular deaths were adjudicated by clinical events committee through 2 years for the randomized cohorts and through 1 year for the registry cohorts and were subsequently site reported; because of inconsistently applied definitions of heart failure hospitalization between the clinical events committee and sites, only clinical events committee adjudicated cases of heart failure hospitalization have been included in the current analysis. The analysis population was restricted to patients with core lab assessed baseline echocardiographic data, including LVEF assessment by Simpson method. Informed consent was signed by each participant, and institutional review boards granted approval for the study at each site.

Echocardiographic Assessment

Transthoracic echocardiography was performed at baseline, before discharge, and at 1-month, 1-year, and 2-year visits. All echocardiograms were independently analyzed by an echocardiographic central core lab and chamber parameters were measured according to the American Society of Echocardiography recommendations.[16] Severe AS was

defined as follows: (1) aortic valve area ≤0.8 cm^2 or aortic valve area index ≤0.5 cm^2/m^2 and (2) mean aortic valve gradient >40 mm Hg or peak aortic jet velocity >4.0 m/s at rest or during dobutamine infusion. Image acquisition and image analysis quality methods were reported in detail previously.[17] LVEF was measured using the biplane Simpson volumetric method combining apical 4-chamber and 2-chamber views. Aortic valve peak and mean gradients were obtained using the view showing the maximal velocity. Aortic and mitral valve measurements including paravalvular regurgitation were measured as described previously.[17]

Study End Points and Definitions

The key end points of interest for the current analysis are cardiovascular mortality, all-cause mortality, and heart failure hospitalization, assessed out to 2 years after the procedure. All-cause and cardiovascular mortality were defined according to the Valve Academic Research Consortium-2 consensus.[18] Heart failure hospitalization was protocol-defined as rehospitalization for symptoms of aortic valve stenosis or complications of the index procedure. Definitions of additional end points were reported in the primary publications.[9] Patients were stratified according to whether or not they had reduced LVEF (defined as LVEF <50%).[19,20] Sensitivity analyses modeled LVEF as a continuous linear variable and further stratified patients to 3 categories: low (LVEF <30%), intermediate (LVEF 30%–50%), or high (LVEF≥50%) LVEF. In addition, we examined the change of LVEF at 1-month in each of these 3-groups.

Statistical Analysis

Categorical variables were compared using the Fisher exact test. Continuous variables were presented as median with 25% and 75% interquartile range and compared using Wilcoxon rank sum test test. Survival curves for time-to-event of all-cause mortality, cardiovascular mortality, and heart failure hospitalizations were constructed using Kaplan–Meier estimates, which were compared using the log-rank test.

Multivariable Cox proportional hazards regression assessed the adjusted relationship between LVEF and clinical outcomes during 2 years follow-up. The main model treated LVEF as a continuous variable, and the following covariates were included: sex, age, creatinine clearance, diabetes mellitus, peripheral vascular disease, prior stroke, chronic obstructive pulmonary disease, oxygen use, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass surgery, extent of coronary disease, smoking, pacemaker, access site, moderate-severe mitral regurgitation and tricuspid regurgitation, and mean aortic gradient. Additional models were performed, including all of the above and stroke volume index (SVi), as well as models treating LVEF as a categorical variable with 2 categories and 3 categories. Stratification by study was performed for all models. The relationship between baseline LVEF and the risk of all-cause and cardiovascular mortality was further explored by entering LVEF as a nonlinear term (penalized spline with 2 *df*) in Cox proportional hazards regression models.[21,22] The effect of LVEF change at 30 days postprocedure on outcomes was assessed by entering LVEF in a similar multivariable model which included adjustment to all of the covariates mentioned above including SVi with the addition of baseline LVEF and this consistency of risk was assessed among baseline low and normal LVEF groups using interaction testing. LVEF improvement was analyzed using a matched pairs analysis, and comparisons were performed by paired *t* test.

All statistical analyses were performed with the use of SAS software version 9.4. Statistical significance in final models was defined by a $P<0.05$.

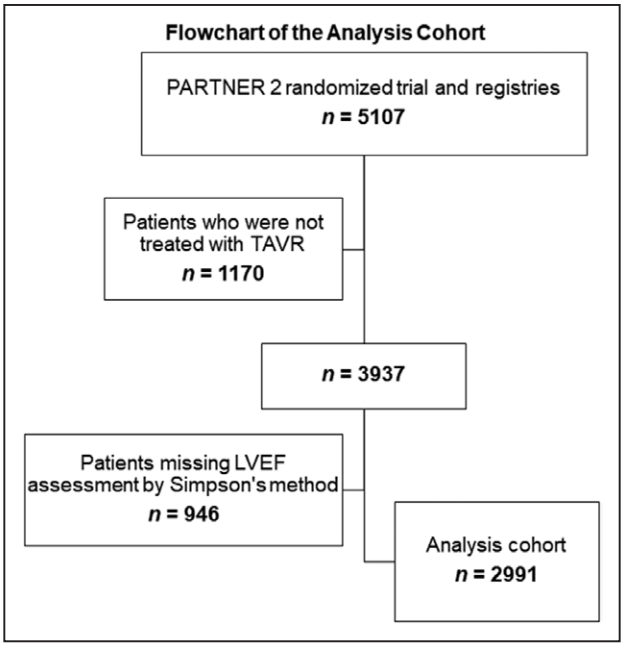

Figure 1. Flowchart of the analysis cohort.
LVEF indicates left ventricular ejection fraction; PARTNER 2, Placement of Aortic Transcatheter Valves; TAVR, transcatheter aortic valve replacement.

RESULTS

Subject Characteristics

Of the 2991 pooled patients who underwent TAVR and had complete baseline echocardiographic data (Figure 1), 28% were categorized to the reduced LVEF group (LVEF<50%). Table 1 compares the baseline characteristics of patients in the 2 groups. Mean baseline LVEF in the pooled cohort was 55.8±13.3% for those with preserved LV function and was 38.1±8.7% in the low LVEF group. Patients with LV dysfunction were more frequently males, had lower BMI, and a higher prevalence of diabetes mellitus, chronic renal insufficiency, history of coronary artery disease, previous myocardial infarction, and peripheral vascular disease. Pacemaker and automated implantable cardiovascular defibrillator implantation rates were more frequently present among impaired LV dysfunction patients. The STS risk score was also significantly higher in the low LVEF group. Comparison of medications use is available in Table I in the Data Supplement.

Table 1. Baseline Characteristics Stratified by LVEF

	EF<50% (n=839)	EF≥50% (n=2152)	Total (n=2991)	*P* Value
Age, y	83 [78–87]	84 [79–88]	84 [79–88]	0.08
Male, n (%)	603 (71.9)	1061 (49.3)	1664 (55.6)	<0.0001
BMI, kg/m^2	26.0 [23.5–29.7]	27.1 [23.8–31.0]	26.7 [23.7–30.7]	<0.0001
Prior myocardial infarction	230 (27.4)	287 (13.3)	517 (17.3)	<0.0001
Prior CABG, n (%)	358 (42.7)	508 (23.6)	866 (29.0)	<0.0001
Prior PCI, n (%)	295 (35.2)	623 (28.9)	918 (30.7)	0.0009
Coronary artery disease, n (%)	725 (86.4)	1570 (73.0)	2295 (76.7)	<0.0001
Syntax score	2.0 [0.0–9.0]	0.0 [0.0–7.0]	0.0 [0.0–7.0]	0.13
Peripheral vascular disease, n (%)	301 (35.9)	647 (30.1)	948 (31.7)	0.002
Hypertension, n (%)	775 (92.4)	1981 (92.1)	2756 (92.1)	0.77
Dyslipidemia, n (%)	682 (81.3)	1700 (79.0)	2382 (79.6)	0.16
Smoking (previous or current), n (%)	448 (53.4)	1050 (48.8)	1498 (50.1)	0.02
COPD, n (%)	271 (32.3)	690 (32.2)	961 (32.2)	0.96
Oxygen-dependent lung disease, n (%)	48 (5.7)	169 (7.9)	217 (7.3)	0.04
Diabetes mellitus, n (%)	314 (37.4)	706 (32.8)	1020 (34.1)	0.02
Prior stroke or TIA, n (%)	153 (18.2)	400 (18.6)	553 (18.5)	0.82
NYHA functional class III or IV, n (%)	733 (87.4)	1719 (79.9)	2452 (82.0)	<0.0001
Renal insufficiency (SCr ≥2 mg/dL), n (%)	113 (13.5)	150 (7.0)	263 (8.8)	<0.0001
Permanent pacemaker, n (%)	183 (21.8)	256 (11.9)	439 (14.7)	<0.0001
AICD, n (%)	24 (6.6)	15 (1.3)	39 (2.6)	<0.0001
STS risk score	7.3 [5.2–10.3]	6.0 [4.5–8.4]	6.3 [4.7–9.0]	<0.0001
Echocardiographic characteristics				
Aortic valve area index, cm^2/m^2	0.34 [0.29–0.42]	0.37 [0.31–0.43]	0.37 [0.31–0.43]	<0.0001
Peak AV gradient, mm Hg	67 [54–78]	76 [65–91]	73 [62–88]	<0.0001
Peak AV velocity, cm/s	408 [366–445]	435 [403–476]	427 [395–469]	<0.0001
Mean aortic valve gradient, mm Hg	39 [31–47]	45 [38–54]	43 [36–52]	<0.0001
LV ejection fraction, %	40 [32–45]	62 [57–68]	59 [48–65]	<0.0001
Aortic insufficiency (severe), n (%)	24 (3.0)	30 (1.4)	54 (1.8)	0.005
Mitral insufficiency (moderate-severe), n (%)	224 (28.2)	287 (13.8)	511 (17.8)	<0.0001
Tricuspid insufficiency (severe), n (%)	34 (4.5)	36 (1.8)	70 (2.5)	<0.0001
Left ventricle stroke volume index, mL/m^2	26 [21–32]	31 [26–37]	30 [25–36]	<0.0001
Procedural characteristics				
Access site, n (%)				
Femoral	647 (77.2)	1757 (81.7)	2404 (80.4)	0.006
Transaortic	61 (7.3)	115 (5.3)	176 (5.9)	0.04
Transapical	130 (15.5)	279 (13.0)	409 (13.7)	0.07

AICD indicates automated implantable cardiovascular defibrillator; AV, aortic valve; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SCr, serum creatinine; STS, Society of Thoracic Surgeons; and TIA, transient ischemic attack.

Baseline Echocardiographic Characteristics

Moderate or severe mitral regurgitation was more common in those with LV dysfunction, and they also had lower mean and peak aortic valve gradients and smaller indexed aortic valve areas on baseline rest echocardiographic studies. We included characteristics of patients who did not have available Simpson evaluation of LVEF in Table II in the Data Supplement.

Analysis of the Association of Clinical End Points With LVEF

A total of 600 patients died during the 2-year period after the procedure, of which 386 deaths were of cardiovascular cause. In the reduced LVEF group, higher rates of both 2-year all-cause (27.4% versus 19.2%, *P*<0.0001) and cardiovascular mortality (19.8% versus 12.0%, *P*<0.0001) were recorded (Table 2). The 2-year

Table 2. Two-Years Clinical Outcomes Comparing Reduced (<50%) With Normal LVEF Groups

Clinical Outcomes	EF<50%, n (%)	EF≥50%, n (%)	Unadjusted HR (95% CI)	*P* Value
All-cause mortality	213 (27.4)	387 (19.2)	1.53 (1.29–1.81)	<0.0001
Cardiovascular mortality	149 (19.8)	237 (12.0)	1.74 (1.41–2.13)	<0.0001
Noncardiovascular mortality	64 (9.4)	150 (8.1)	1.07 (0.79–1.43)	0.67
Heart failure hospitalizations	187 (33.6)	359 (23.9)	1.44 (1.21–1.72)	<0.0001
CVA/TIA	72 (9.8)	222 (11.4)	0.87 (0.67–1.13)	0.30

CVA indicates cerebrovascular accident; EF, ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; and TIA, transient ischemic attack.

rate of heart failure hospitalizations was also higher among patients with LV dysfunction (33.6% versus 23.9%, *P*<0.0001), whereas no statistically significant difference was seen with respect to cerebrovascular accidents or transient ischemic attacks between the 2 groups (Table 2). There was no statistically significant difference between the groups in respect to 30 days postprocedural moderate to severe paravalvular leak rates, as well as new pacemaker implantation (Table III in the Data Supplement). When LVEF was categorized to low and normal groups, both 2-year cardiovascular and all-cause mortality, as well as heart failure hospitalization rates increased with the degree of LV function impairment (Figure 2A through 2C). Similar results were seen when LVEF was categorized as a 3-level variable (low, intermediate, and normal LVEF; Figure IA through IC and Table IV in the Data Supplement). Thirty-day clinical outcomes comparing reduced and normal LVEF groups are presented separately (Table V in the Data Supplement).

After multivariable adjustment, reduced versus normal LVEF was independently associated with increased risk of 2-year cardiovascular death, whereas the risk of all-cause mortality approached but did not meet statistical significance; no significant association with heart failure hospitalizations was found (Table 3). Similarly, LVEF modeled as a continuous term was independently associated with 2-year cardiovascular death and also

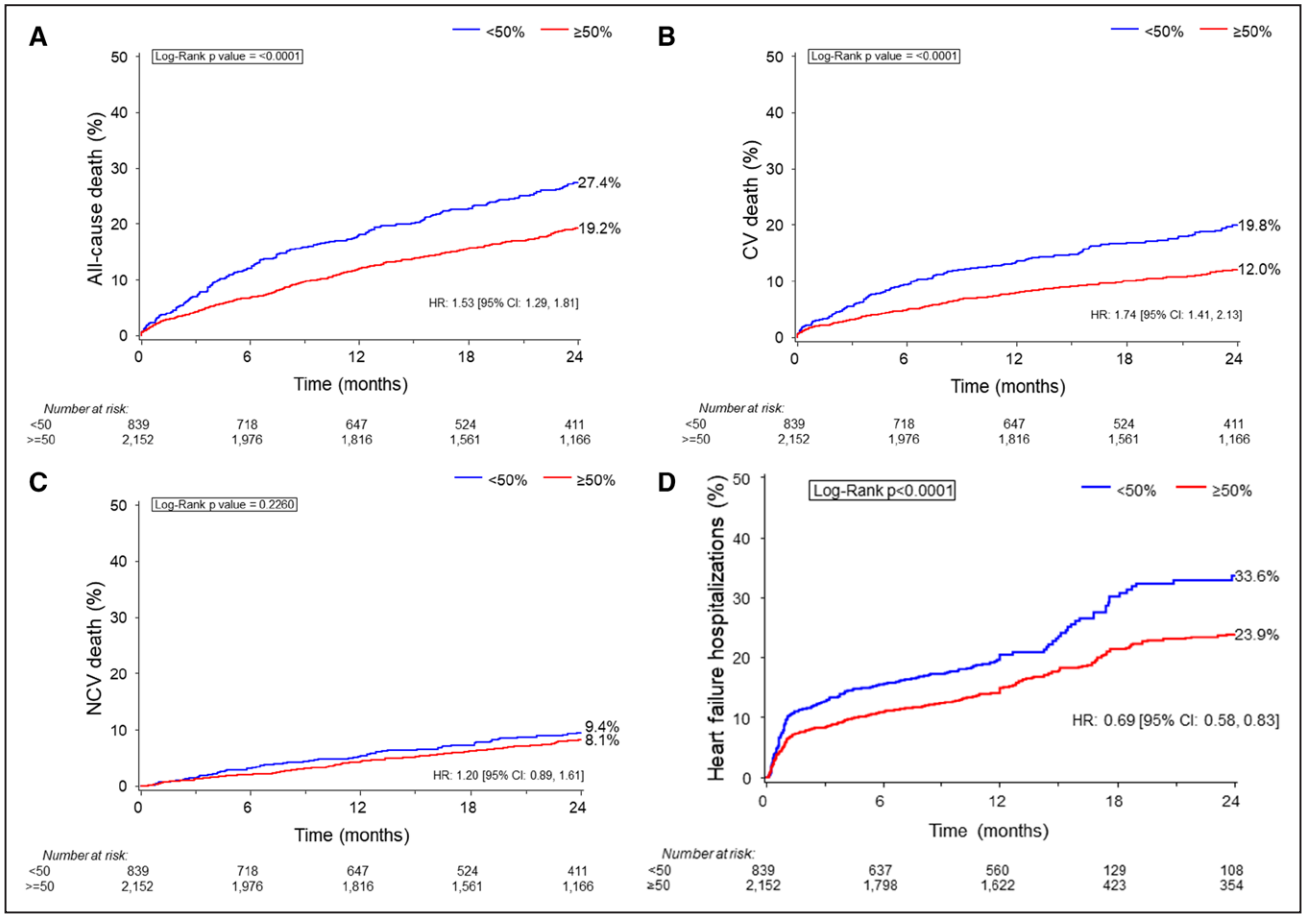

Figure 2. Kaplan–Meier curves of patients categorized to low (<50%) and normal (≥50%) left ventricular ejection fraction groups.
A, All-cause mortality; (**B**) cardiovascular (CV) mortality; (**C**) non-cardiovascular (NCV) mortality; (**D**) heart failure rehospitalization. HR indicates hazard ratio.

Table 3. Independent Predictors of 2-Year Clinical Outcomes, LVEF Treated as Dichotomous Variable

	Adjusted HR (95% CI)	*P* Value
2-year all-cause mortality		
Baseline LVEF <50%	1.20 (0.99–1.47)	0.07
Mean aortic valve gradient (per 10 mm Hg increase)	1.01 (0.94–1.07)	0.88
2-year cardiovascular mortality		
Baseline LVEF <50%	1.42 (1.11–1.81)	0.005
Mean aortic valve gradient (per 10 mm Hg increase)	0.96 (0.88–1.04)	0.31
2-year noncardiovascular mortality		
Baseline LVEF <50%	0.77 (0.57–1.04)	0.09
Mean aortic valve gradient (per 10 mm Hg increase)	1.06 (0.97–1.16)	0.21
2-year heart failure hospitalizations		
Baseline LVEF <50%	1.16 (0.94–1.43)	0.17
Mean aortic valve gradient (per 10 mm Hg increase)	0.93 (0.86–0.99)	0.03

Adjusted for the following: sex, age, creatinine clearance, diabetes mellitus, peripheral vascular disease, prior stroke, COPD, oxygen use, prior MI, prior PCI, prior CABG, extent of coronary disease, smoking, pacemaker, access site, moderate-severe MR and TR, and mean aortic gradient (continuous) and stratified by study. CABG indicates coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; and TR, tricuspid regurgitation.

Table 4. Independent Predictors of 2-Year Clinical Outcomes, LVEF Treated as Continuous Variable

	Adjusted HR (95% CI)	*P* Value
2-year all-cause mortality		
Baseline LVEF (per 10% decrease)	1.09 (1.01–1.16)	0.02
Mean aortic valve gradient (per 10 mm Hg increase)	1.01 (0.94–1.08)	0.79
2-year cardiovascular mortality		
Baseline LVEF (per 10% decrease)	1.16 (1.07–1.27)	0.0006
Mean aortic valve gradient (per 10 mm Hg increase)	0.96 (0.89–1.05)	0.40
2-year noncardiovascular mortality		
Baseline LVEF (per 10% decrease)	0.93 (0.83–1.03)	0.15
Mean aortic valve gradient (per 10 mm Hg increase)	1.06 (0.97–1.16)	0.20
2-year heart failure hospitalizations		
Baseline LVEF (per 10% decrease)	1.06 (0.99–1.14)	0.11
Mean aortic valve gradient (per 10 mm Hg increase)	0.93 (0.86–1.00)	0.04

Adjusted for the following: sex, age, creatinine clearance, diabetes mellitus, peripheral vascular disease, prior stroke, COPD, oxygen use, prior MI, prior PCI, prior CABG, extent of coronary disease, smoking, pacemaker, access site, moderate-severe MR and TR, and mean aortic gradient (continuous) and stratified by study. CABG indicates coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; and TR, tricuspid regurgitation.

reached significance with respect to all-cause death (Table 4). Aortic valve gradient was not associated with cardiovascular or all-cause mortality in either model, but a significant association was found with respect to heart failure hospitalizations (hazard ratio per 10 mm Hg increase, 0.93 for both models; 95% CI, 0.86–0.99 in Model 1 and 0.86–1.00 in Model 2). An additional model with LVEF treated as 3-way variable is presented in Table VI in the Data Supplement. When SVi was added as a covariate to the main model, the results were consistent with previous findings with respect to LVEF, and SVi was found to be an additional independent predictor of all-cause mortality, but not cardiovascular mortality or heart failure hospitalizations (Table VII in the Data Supplement).

Adjusted spline analysis demonstrated a near-linear association between LVEF level and all-cause mortality during 2 years follow-up (*P*=0.61 for the nonlinear term; Figure IIA in the Data Supplement) which was driven by cardiovascular mortality (*P*=0.19 for the nonlinear term; Figure IIB in the Data Supplement). For both end points, the risk increased with increasing reduction in LVEF.

LVEF improved in 30 days from a mean of 24.7±4.3% to 32.2±9.6% in the group with baseline LVEF lower than 30%, from 41.5±5.7% to 45.7±9.6% in the group with baseline LVEF≥30% and lower than 50%, and decreased from 62.7±7.0% to 61.8±8.2% in the group with baseline LVEF≥50%. When included in a multivariable model (with addition of baseline LVEF as covariate), LVEF change within 30 days was significantly associated with cardiovascular mortality (hazard ratio for 10% increase in EF, 0.79 [0.66–0.94], *P*=0.01; (Figure III in the Data Supplement). The effect was consistent among patients with low and normal baseline LVEF ($P_{interaction}$=0.98).

DISCUSSION

The main finding of this individual patient-level pooled analysis of patients with severe AS who underwent TAVR in the PARTNER 2 trial and registries is that compared with patients with normal LVEF those with reduced LVEF were at higher risk for short term cardiovascular mortality.

LV dysfunction is a well-established poor prognostic factor in patients with severe AS. Reduced LVEF was previously found to be associated with a higher proportion of adverse outcomes in patients who were treated medically.[1] Although SAVR has shown survival benefit compared with medical treatment for patients with impaired LV function, their outcomes remain substantially worse than those of patients with normal EF.[2]

TAVR intervention has been shown to portend better outcomes in high-risk patients compared with medical treatment and comparable outcomes to SAVR.[11,23–25] However, the role of low preprocedural LVEF as an independent prognostic factor among TAVR patients remains unresolved.[13,26,27] Post hoc analyses of the PARTNER IA[17,28] and IB[1] trials, the combined IA and B study,[27] as well as observational studies,[26,29] found that baseline LVEF was not predictive of 1-year outcomes. More recently, an analysis performed on a large registry of TAVR patients also suggested LVEF was not an independent factor predicting adverse clinical outcomes.[14] Conversely, 2 large meta-analyses[13,30] based on nonrandomized studies did find a significant difference between low-EF and normal-EF groups in respect to 1-year mortality. LVEF recovery 30 days after TAVR among patients with baseline LVEF dysfunction was found to be associated with decreased all-cause mortality, but not cardiovascular mortality in an analysis of PARTNER cohort A.[28] Although we found that 30 days change in LVEF was associated with cardiovascular mortality, no significant interaction was found between change among low and normal baseline LVEF groups.

Possible explanations for the conflicting results might be related to the fact that previous trials either used nonrandomized data,[13,14,26,29–31] lacked power because of smaller sample size,[17,26,28,29,31] or lacked independent adjudication of clinical outcomes and validated core lab analysis of echocardiograms.[13,14,26,29–31] In addition, EF in the PARTNER I trial using core lab analysis used visual EF in 44%[28] of TAVR cases. The current study presents a large cohort of intermediate and high-risk patients who were treated with contemporary TAVR devices and that were included in prospective trials, with independent adjudication for cause of death and central echocardiographic core lab analysis using the guideline-recommended method of biplane Simpson EF measurements. Thus, a narrower variance in measurements improved accuracy of baseline LVEF assessment. In addition, when compared with the high-risk cohort in PARTNER I analyses, it is important to note that most of the patients in the current analysis were categorized as intermediate risk patients. It is possible that among high-risk patients there was a higher proportion of patients with impaired LV function and preserved EF (heart failure with preserved ejection fraction) that were included in the normal-EF group and that these patients were present in a smaller proportion among the normal-EF population in the current comparison. The prevalence of this subset of patients was hypothesized as one of the reasons for failing to prove a prognostic effect for LVEF in the PARTNER IA subanalysis.[28] Thus, it is possible that a diminished proportion in the current analysis could explain the differing results. In addition, compared with previous analyses of randomized data, we have been able to report a relatively large cohort of patients with low LVEF.

To minimize the risk of confounding effect and facilitate cross-trial comparisons, we have adopted a multivariable model that included most of the clinical and echocardiographic variables that were included in a large previous report, although this study did not include SVi.[14] In particular, we found that mean aortic valve gradient did not have a significant independent effect on outcomes, in contrast to previous studies,[14,27] whereas our results suggest LVEF is a more powerful prognostic factor. In the current analysis, 13% of all patients (and 44.6% of low-EF patients) had reduced LVEF and gradient >40 mm Hg. Likewise, in a large registry report, the median gradient of patients with LVEF between 30% and 50% was 41 mm Hg, indicating at least half of the patients had both impaired LVEF and high aortic gradient.[14] These figures accentuate the fact that there is a substantial portion of patients who already have impaired LV function, which is associated with increased mortality, but still the LV is capable of generating an adequate pressure to overcome the valvular resistance and thus present with increased transvalvular gradient. Differences in outcomes might already be witnessed at this point before further myocardial decline would lead to reduced gradient.

In contrast to long-term mortality, we were unable to show a significant independent association of heart failure hospitalizations with baseline LVEF. This finding is surprising as this rate is expected be higher in patients with an impaired LV function. Of note, however, is that the definition of rehospitalizations in the current analysis includes only rehospitalizations for symptoms of AS or complications of the procedure. Recently, it was reported that heart failure rehospitalization constitutes only a small fraction of the causes for readmissions,[32] and therefore this end point does not suffice to represent the differences in heart failure severity between the 2 groups.

Clinical Implications

The results reported here should be taken with caution when considering clinical implications because of the nature of this post hoc analysis and the use of clinical end points that other than the primary ones in the original study. Nevertheless, the current study suggests an important role for baseline LVEF as a measurement of LV dysfunction when considering the right timing for intervention. It is possible that an earlier intervention using higher LVEF cutoff value is warranted to avoid a procedure in a patient with deteriorated left ventricle resulting in worse outcomes. A recent report suggested to revisit the optimal cutoff of LVEF in AS patients and to use a cutoff value of 60% in this population as a marker of ventricular dysfunction.[33] In addition, further evaluation of the cause for low LVEF

(even in the presence of normal gradient, in addition to current guidelines recommendation[34]) among these patients could help to better delineate the cause of low LVEF and make more precise patient selection based on predicted long-term outcomes.[35] However, it must be noted that despite the apparently poorer prognosis expected for these patients, they still seem to have a more favorable outcome compared with low-EF patients treated medically, who have almost twice the risk of 1-year all-cause mortality.[1]

From a pathophysiologic point of view, the explanation for low LVEF is similar to that previously described for low flow states[27] and comprises either afterload mismatch,[36] intrinsic myocardial damage, or both. The distinction between the two could be of immense clinical importance and should be considered in patient selection for mechanical intervention in the aortic valve. For patients presenting with low EF due to increased afterload mismatch, arising in most cases from progression of valvular stenosis (and to some degree by changes in vascular properties), the ventricular response begins with hypertrophy, maintaining normal EF, but with deterioration and progression of valve stenosis, myocardial fibrosis becomes dominant and EF declines. In such cases, it is expected that removal of the cause for increased afterload could result in some recovery of ventricular function. However, where the reduced ejection function is mainly caused by intrinsic myocardial damage, reduction of afterload by mechanical valve intervention is not expected to result in similar recovery, and these patients probably bear dismal prognosis. Barbash et al[26] demonstrated that among TAVR patients with poor cardiac reserve (as assessed by dobutamine test), in-hospital mortality was up to 6-fold higher, compared with patients who were found to have cardiac reserve, but no significant difference was observed in respect to 1-year mortality. Unfortunately, we do not have enough information on the cause of low LVEF in our cohort, and future-focused research to compare in-group outcomes based on cardiac reserve is needed to confirm this hypothesis.

Limitations

First, this is a post hoc analysis of data pooled from 4 prospective trials. However, the trials had similar design and low rates of lost to follow-up, and analyses were stratified by study to account for potential within-study clustering effects. In addition, we lack data on the cause of decreased LVEF, and we thus cannot differentiate between the various causes and the prediction of mortality by LVEF. Finally, we do not have data on whether the low-EF patients received optimal medical care, including implantable cardiovascular defibrillator implantation and cardiac resynchronization therapy when indicated.

Conclusions

Baseline LVEF measured by biplane Simpson method predicts 2-year cardiovascular mortality. LVEF may be an important consideration when determining the appropriate timing of intervention on severe, symptomatic AS.

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